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Calcium antagonists are associated with reduced mortality after cardiac surgery: A propensity analysis

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Objectives: Observational studies have questioned the effectiveness of perioperative calcium channel blockers but failed to correct for selection biases. We therefore performed a prospective observational cohort study of the effects of calcium channel blockers on cardiac surgical mortality. A propensity score technique was used for risk adjustment.

Methods: We identified 6619 patients who underwent nontransplant cardiac surgery at the Toronto General Hospital (Toronto, Ontario, Canada) between May 1999 and December 2001. Propensity scores for calcium channel blocker use were constructed for the entire sample and for the subgroup (n = 5222) that underwent coronary artery bypass grafting. The calcium channel blocker adjusted odds ratio for in-hospital mortality after cardiac surgery was determined by using multiple logistic regression and propensity matched-pairs analyses. A subgroup analysis was performed for patients who underwent coronary artery bypass grafting: the calcium channel blocker adjusted odds ratio for mortality was determined by using propensity score matched-pairs analyses.

Results: Calcium channel blockers were associated with significantly reduced cardiac surgical mortality after adjustment with both multiple logistic regression (odds ratio, 0.56; 95% confidence interval, 0.33-0.94; $P = .028$) and propensity score matched-pairs analyses (odds ratio, 0.56; 95% confidence interval, 0.32-0.98; $P = .042$). Calcium channel blockers were also associated with reduced mortality (odds ratio, 0.48; 95% confidence interval, 0.23-0.98; $P = .044$) among patients who underwent coronary artery bypass grafting.

Conclusions: After adjustment for baseline differences, calcium channel blockers were associated with significantly reduced mortality after cardiac surgery. This benefit also extends to the subgroup that underwent coronary artery bypass grafting. A large randomized controlled trial of perioperative calcium channel blockers is therefore warranted.

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The role of calcium channel blockers (CCBs) in cardiac surgery is controversial. Prior observational studies concluded that CCBs did not reduce mortality[1] or myocardial ischemia.[2,3] In contrast, a recent meta-analysis of randomized controlled trials (RCTs) found that CCBs significantly reduced perioperative myocardial infarction (MI) and ischemia during cardiac surgery;[4] however, the study was underpowered to determine effects on mortality.

CCBs have multiple benefits that explain the findings of the meta-analysis. They improve balance between myocardial oxygen supply and demand through negative chronotropic, negative inotropic, afterload-reducing, and coronary vasodilatatory properties. Imbalance between myocardial oxygen supply and demand might cause ischemia and MI.[5] CCB-mediated vasodilatation might reduce coronary artery bypass graft (CABG) spasm, another cause of postoperative ischemia. Nondihydropyridine CCBs have also been shown to prevent supraventricular tachyarrhythmias in both animal studies[6] and the recent meta-analysis.[4] They might therefore reduce postoperative atrial fibrillation, which is associated with neurocognitive dysfunction[7] and prolonged hospitalization.[8]

The cause of the discrepancies between RCTs and observational studies might be inadequate risk adjustment for important selection biases. Patients receiving CCBs are likely to be older, with more chronic obstructive pulmonary disease, peripheral vascular disease, and diabetes mellitus. These systemic diseases increase cardiac surgical mortality.[9] Furthermore, they reduce the likelihood of receiving β-blockers,[10] which reduce mortality after CABG surgery.[11] Indeed, only 30% of patients who receive CCBs after MI will receive β-blockers concurrently.[10] Furthermore, CCB users might have more severe coronary artery disease that failed symptomatic control with β-blockers alone. Failure to adjust for these selection biases will prevent identification of the treatment effects of CCBs.

We therefore undertook a prospective observational cohort study of cardiac surgical patients, aiming to determine the effects of CCBs on in-hospital mortality while adjusting for selection biases with propensity score techniques.[12]

Methods

Patient Population and Data Sources

Preoperative, intraoperative, and postoperative information for individuals undergoing cardiac surgery at the Toronto General Hospital, University Health Network (Toronto, Ontario, Canada), was prospectively collected in cardiac surgery and anesthesia registries, with the approval of the institutional research ethics board. These databases have been previously described.[13,14] The databases document CCB and β-blocker use in the preoperative period but not in the intraoperative or postoperative periods. All cardiac surgical patients at the Toronto General Hospital routinely receive their last preoperative dose of cardiac medication on the morning of the operation.

The study sample consisted of individuals who underwent nontransplant cardiac surgical procedures between May 1, 1999, and December 31, 2001. A total of 6635 individuals underwent eligible procedures. We excluded 16 (0.2%) patients with missing preoperative medication data. Ninety-two (1.4%) patients had missing data in elements aside from preoperative medications. An unknown left ventricular ejection fraction was considered equal to a normal ejection fraction (>60%), a previously used approach[15] recommended by Pierpont and associates.[16] Missing values for dichotomous variables were assigned the most frequent value, whereas continuous variables were assigned the median value, as previously described.[11] Reanalysis after exclusion of patients with missing data did not materially alter the results.

General Analysis Issues

All analyses were performed with SAS Version 8.20 software (SAS Institute, Cary, NC).

Propensity Score Development

Given that CCB therapy assignment was nonrandom, confounding and selection biases were accounted for through a propensity score for CCB use. The rationale and methods underlying the use of propensity scores for proposed causal exposure variables have been previously described.[17] Multiple logistic regression[18] was used to construct a propensity score for preoperative CCB use, without regard for outcome. We developed a full nonparsimonious model, including 26 covariates and 18 first-order interactions (Table 1). This model had an area under the receiver operating characteristic (ROC) curve of 0.73.

Multiple Logistic Regression Risk Adjustment

The effects of CCBs and β-blockers on in-hospital mortality were determined by using multiple logistic regression. Treatment effects were adjusted by using the following covariates: year, age, sex, left ventricular ejection fraction (>60%, 40%-60%, 20%-40%, and <20%), procedure (CABG, single-valve surgery, and complex procedures), prior cardiac surgery, timing of operation, triple-vessel coronary disease (stenoses >70% in 3 major coronary arteries), left main coronary artery disease (stenosis >50%), MI within 30 days, Canadian Cardiovascular Society class IV angina, preoperative intra-aortic balloon pump support, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, and chronic obstructive pulmonary disease. Operation timing was graded as follows: elective, semiurgent (cannot leave hospital without surgical intervention), urgent (surgical intervention required within 72 hours of presentation), and emergency (surgical intervention required within 12 hours of presentation).

Three models were generated. The first model consisted of the risk-adjustment covariates alone. The second model consisted of the risk-adjustment covariates, CCB use, and β-blocker use. The third model consisted of the risk-adjustment covariates, CCB use, β-blocker use, and propensity score. We calculated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for CCB and β-blocker use in the 2 latter regression models.

Combined CCB and β-blocker use might represent a harmful interaction given their combined negative inotropic effects. We therefore tested the statistical significance of adding an interaction term between CCBs and β-blockers in the third regression model.

The models' discrimination and calibration were determined by using ROC curve areas and Hosmer-Lemeshow goodness-of-fit statistics, respectively.[18]

Propensity Score Matched-Pairs Analysis

To determine the robustness of the results from model-based risk-adjustment techniques, we also calculated the treatment effects of CCBs by using a matched-pairs analysis. Using an SAS

TABLE 1. Propensity score model for entire study sample

Covariates	Interaction terms
Year	Year × procedure type
Age	Age × sex
Sex	Age × left ventricular ejection fraction
Body surface area	Age × timing of operation
New York Heart Association class	Age × procedure type
Triple-vessel coronary artery disease	Age × repeat operation
Left main coronary artery disease	Left ventricular ejection fraction × timing of operation
Left ventricular ejection fraction	Left ventricular ejection fraction × procedure type
MI within 30 d	Left ventricular ejection fraction × repeat operation
Cerebrovascular disease	Left ventricular ejection fraction × hypertension
Peripheral vascular disease	Procedure type × triple-vessel coronary artery disease
Prior PTCA	Procedure type × β-blocker use
Positive stress test result	Procedure type × inhaled bronchodilator use
Prior thrombolysis	MI within 30 days × repeat operation
Diabetes mellitus	Peripheral vascular disease × New York Heart Association class
Hypercholesterolemia	Positive stress test result × procedure type
Hypertension	Positive stress test result × prior PTCA
Current smoker	Positive stress test result × left ventricular ejection fraction
Preoperative hemoglobin concentration	
Preoperative serum creatinine concentration	
β-Blocker use	
Inhaled bronchodilator use	
Angiotensin-converting enzyme inhibitor use	
Repeat operation	
Timing of operation	
Procedure type	

PTCA, Percutaneous transluminal coronary angioplasty.

macro (available at www2.sas.com/proceedings/sugi26/p214-26.pdf), we matched CCB users to unique control subjects by using their propensity scores.* We attempted to match each CCB user to a non-CCB user with a propensity score identical to 5 digits. If this was not possible, we attempted 4-, 3-, 2-, and 1-digit matches. Once this threshold was passed, that specific CCB user was excluded.

Conditional logistic regression was used to determine the effects of CCBs on mortality and several postoperative complications: dialysis, low cardiac output state, permanent pacemaker insertion, reoperation, and major bleeding. Low cardiac output state was defined as the need for intra-aortic balloon pump support or inotropic medication (dopamine in excess of 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, dobutamine, milrinone, or epinephrine) for at least 30 minutes to maintain systolic blood pressure of greater than 90 mm Hg and cardiac output of greater than 2.2 $L \cdot min^{-1} \cdot m^{-2}$.[13] Major bleeding was defined as a requirement for more than 10 units of blood during the operative period, chest tube drainage of greater than 2400 mL over 24 hours, or reoperation for significant bleeding.[19]

Subgroup Analyses

CCBs might have different effects among individuals with significant coronary artery disease. We therefore performed a subgroup analysis for patients who underwent CABG with and without any concurrent procedures. This subgroup consisted of 5222 (78.9%) patients.

A propensity score for CCB use within this subgroup was developed by using multiple logistic regression. We developed a full nonparsimonious model, including 24 covariates and 16 first-order interactions; these variables are available from the authors. The ROC area for this model was 0.68. Matched pairs were generated on the basis of propensity scores, as described above. Conditional logistic regression modeling was used to determine the effects of CCBs on mortality, dialysis, low cardiac output state, permanent pacemaker insertion, reoperation, and major bleeding.

Sensitivity Analyses

Given that β-blockers are associated with reduced mortality after CABG,[11] we carried out sensitivity analyses to determine whether preoperative β-blocker use affected the treatment effects of CCBs. Patients who underwent CABG were further divided into 2 subgroups defined by whether they were or were not receiving β-blockers preoperatively. We used multiple logistic regression to determine the adjusted effects of CCBs on mortality within each subgroup. Although age, sex, and CCB use were forced into the models, forward stepwise selection was used to identify other covariates. We used stepwise selection because of the limited statistical power of the subgroups. The covariates considered were year, left ventricular ejection fraction, procedure other than CABG, prior cardiac surgery, timing of operation, triple-vessel coronary disease, left main coronary artery disease, MI within 30

* Parsons LS. Reducing bias in a propensity score matched-pair sample by using greedy matching techniques. Presented at the 26th Meeting of SAS Users' Group International (SUGI 26); April 22-25, 2001; Long Beach, Calif.

TABLE 2. Baseline characteristics of study sample

Variables	Entire study sample			Propensity-matched pairs		
	CCB (n = 2097)	No CCB (n = 4522)	*P* value	CCB (n = 1890)	No CCB (n = 1890)	*P* value
Demographic						
Age, y (mean)	65	60	<.0001	65	64	.51
Body surface area, m^2 (mean)	1.92	1.90	.005	1.92	1.91	.73
Female sex (%)	25.9	26.9	.38	24.8	26.1	.35
Preoperative cardiac status (%)						
New York Heart Association class IV	49.9	46.3	.0064	50.3	51.9	.35
Triple-vessel disease	54.4	39.7	<.0001	53.2	52.2	.56
Left main coronary artery disease	18.0	14.7	.0007	17.7	17.9	.86
Left ventricular ejection fraction						
>60%	42.8	43.8	.0003	41.4	42.8	.77
40%-60%	39.3	35.1		39.5	38.6	
20%-40%	16.0	17.8		16.9	16.7	
<20%	2.0	3.4		2.2	1.9	
Congestive heart failure	15.4	23.0	<.0001	16.4	17.7	.30
MI within 30 d	13.8	16.7	.003	14.9	14.9	.93
Preoperative intra-aortic balloon pump	1.6	2.4	.035	1.7	2.1	.40
Cerebrovascular disease	10.1	8.6	.054	9.5	10.6	.26
Peripheral vascular disease	17.6	11.3	<.0001	16.1	16.7	.60
Comorbid disease (%)						
Diabetes mellitus	30.9	22.9	<.0001	30.1	30.1	.97
Renal dysfunction	9.6	7.9	.023	9.6	8.3	.17
Preoperative dialysis	0.86	0.73	.58	0.9	1.0	.73
Chronic obstructive pulmonary disease	5.5	3.5	.0001	5.0	4.4	.44
Preoperative medications (%)						
β-Blockers	67.5	62.6	<.0001	70.2	70.1	.94
Angiotensin-converting enzyme inhibitors	41.7	44.5	.029	43.3	43.4	.97
Operative details (%)						
Repeat operation	6.7	8.8	.0036	6.4	6.3	.89
Surgical status						
Elective	58.2	56.7	<.0001	56.8	55.6	.89
Semi-urgent	36.1	34.0		36.8	37.8	
Urgent	5.1	6.2		5.6	5.8	
Emergency	0.7	3.1		0.8	0.9	
Procedure type						
CABG only	81.3	61.3	<.0001	80.6	80.7	.89
Single valve	5.0	14.6		5.5	6.1	
Complex	13.1	24.2		13.9	13.2	

days, Canadian Cardiovascular Society class IV angina, preoperative intra-aortic balloon pump support, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, and chronic obstructive pulmonary disease. A *P* value of less than .05 was required for inclusion.

Results

Patient Characteristics

The study sample consisted of 6619 patients; 31.7% (n = 2097) were receiving CCBs preoperatively. The prevalence of CCB use decreased from 35% in 1999 to 29% in 2001. The in-hospital mortality rate was 1.8% (n = 117). The patients' baseline characteristics are summarized in Table 2. Renal dysfunction was defined as a preoperative creatinine concentration of greater than 130 μmol/L, which is associated with increased perioperative mortality and morbidity.[20]

Multiple Logistic Regression Risk Adjustment

The model consisting of the risk-adjustment covariates alone had an ROC area of 0.85, with good calibration (χ^2 = 6.22, P = .62). CCBs were associated with significant reductions in mortality both before (OR, 0.55; 95% CI, 0.33-0.92; P = .022) and after (OR, 0.56; 95% CI, 0.33-0.94; P = .028) adjustment for propensity score (Table 3). β-Blockers were also associated with significant reductions in mortality in both models (Table 3). The interaction term between CCB use and β-blocker use was statistically nonsignificant (P = .59).

The risk-adjusted model without a propensity score had an ROC area of 0.86, with good calibration (χ^2 = 5.75, P = .68). The model with a propensity score had similar discrimination (ROC area of 0.86) and calibration (χ^2 = 7.16, P = .52).

TABLE 3. Adjusted effects of CCBs and β-blockers

Medication	OR for mortality (95% CI)	*P* Value
Model without propensity score		
CCB	0.55 (0.33-0.92)	.022
β-Blocker	0.52 (0.34-0.79)	.0026
Model with propensity score		
CCB	0.56 (0.33-0.94)	.028
β-Blocker	0.51 (0.33-0.79)	.0023

TABLE 4. Outcomes for propensity score matched pairs

Outcomes	CCB	No CCB	OR	95% CI
Patient no.	1890	1890		
In-hospital mortality (%)	1.01	1.80	0.56	0.32-0.98 (*P*=.042)
Morbidity (%)				
Dialysis	1.01	1.32	0.76	0.42-1.38 (*P*= .37)
Low-output state	4.50	4.29	1.05	0.77-1.45 (*P*= .75)
Permanent pacemaker insertion	2.96	2.54	1.17	0.79-1.73 (*P*= .43)
Repeat operation	5.71	5.03	1.15	0.86-1.53 (*P*= .34)
Major bleeding	4.55	4.50	1.01	0.75-1.37 (*P*= .94)

Propensity Score Matched-Pairs Analysis

Of the 2097 CCB users in the entire study sample, 90% (n = 1890) were matched to unique control subjects. These matched pairs were well balanced for all known covariates (Table 2). The in-hospital mortality rate was 1.4% (n = 53).

Within the matched-pairs sample, CCBs were associated with significant reductions in mortality (OR, 0.56; 95% CI, 0.32-0.98; $P = .042$; Table 4). CCBs were not associated with statistically significant increases in postoperative complications (Table 4).

Subgroup Analyses

The baseline characteristics of the 5222 patients undergoing CABG are summarized in Table 5; 37.1% (n = 1935) were receiving CCBs preoperatively. The in-hospital mortality rate was 1.5% (n = 79).

Of the 1935 CCB users within the CABG subgroup, 89% (n = 1726) were matched to unique control subjects. These matched pairs were well balanced for all known covariates (Table 5). The in-hospital mortality rate for matched pairs was 1.1% (n = 38).

Among the matched pairs, CCBs were associated with significant reductions in mortality (OR, 0.48; 95% CI, 0.23-0.98; $P = .044$; Table 6). CCBs were not associated with statistically significant increases in postoperative complications (Table 6).

Sensitivity Analyses

The CABG subgroup that received β-blockers preoperatively consisted of 3900 patients, of which 35% (n = 1362) were receiving CCBs. The effect of CCBs on mortality among patients receiving β-blockers (Table 7) was similar in magnitude to that determined by matched-pairs analyses (Table 6).

The CABG subgroup that was not receiving β-blockers preoperatively numbered 1322, of which 43% (n = 573) were receiving CCBs. The effect of CCBs on mortality within this subgroup (Table 6) was also similar to that determined by matched-pairs analyses (Table 7).

Discussion

To our knowledge, this is the largest observational study to examine the effects of CCBs on perioperative mortality after cardiac surgery. Approximately 32% of patients were receiving CCBs preoperatively, with use gradually declining from 1999 to 2001. Multiple selection biases determined CCB use, including differences in age, sex, cardiac disease, systemic disease, and preoperative medications. After adjusting for selection biases, CCBs were associated with significantly reduced in-hospital mortality among patients undergoing cardiac surgery, including the subgroup undergoing CABG.

In addition to demonstrating that CCBs were associated with reduced mortality, this study also found that CCBs were free of major side effects. Although CCBs are negative chronotropes, negative inotropes, and platelet inhibitors,[21] we found no evidence that they increased the incidence of related postoperative complications. Furthermore, the benefits of CCBs appeared to be consistent, regardless of whether patients were or were not receiving β-blockers preoperatively.

Comparison With Prior Studies

Our results contradict prior observational studies and support a recent meta-analysis.[4] Two early studies[2,3] looked only at the effects of CCBs on myocardial ischemia, a surrogate outcome, and did not use risk-adjustment techniques. More recently, Weightman and colleagues[1] found that CCBs had no effect on mortality, whereas β-blockers exerted a significant beneficial effect. However, their multiple logistic regression analysis had less statistical power than ours. The power of logistic regression models depends in large part on the number of outcome events.[22] There were only 53 deaths in the study by Weightman and colleagues. In contrast, we used more rigorous statistical risk-adjustment techniques in a sample with 119 deaths.

The recent meta-analysis of preoperative, intraoperative, and postoperative (first 48 hours) CCB use was underpowered to demonstrate significant changes in perioperative mortality.[4] However, CCBs were associated with trends toward decreased mortality among patients undergoing

TABLE 5. Subgroup who underwent CABG

Variables	Entire subgroup CCB (n = 1935)	Entire subgroup No CCB (n = 3287)	Entire subgroup *P* value	Propensity-matched pairs CCB (n = 1726)	Propensity-matched pairs No CCB (n = 1726)	Propensity-matched pairs *P* value
Demographic						
Age, y (mean)	66	63	.0001	65	65	.41
Body, m^2 surface area (mean)	1.92	1.91	.42	1.92	1.92	.76
Female sex (%)	24.3	21.2	.0098	23.9	22.0	.17
Preoperative cardiac status (%)						
New York Heart Association class IV	52.2	56.5	.0026	53.1	53.0	.97
Triple-vessel disease	58.9	54.6	.0030	58.6	58.5	.97
Left main coronary artery disease	19.4	20.1	.54	19.3	19.0	.86
Left ventricular ejection fraction						
>60%	36.9	36.9	<.0001	41.0	40.4	.97
40%-60%	39.6	38.5		39.6	40.4	
20%-40%	16.5	21.3		17.4	17.2	
<20%	2.0	3.4		2.0	2.0	
Congestive heart failure	12.3	16.5	<.0001	12.7	13.9	.29
MI within 30 d	14.9	22.5	<.0001	16.3	15.8	.68
Preoperative intra-aortic balloon pump	1.7	3.1	.0021	1.8	2.1	.54
Cerebrovascular disease	10.2	8.6	.055	9.8	9.8	1.00
Peripheral vascular disease	18.7	14.8	.0002	18.4	17.7	.62
Comorbid disease (%)						
Diabetes mellitus	32.6	29.2	.011	32.2	30.2	.23
Renal dysfunction	9.7	8.2	.062	9.2	8.2	.33
Preoperative dialysis	0.9	0.9	.86	0.9	0.9	1.00
Chronic obstructive pulmonary disease	5.8	4.2	.0063	5.1	4.7	.58
Preoperative medications (%)						
β-Blockers	70.4	77.2	<.0001	74.9	75.0	.94
Angiotensin-converting enzyme inhibitors	42.5	50.4	<.0001	44.2	44.2	.97
Operative details (%)						
Repeat operation	5.3	4.2	.054	4.6	4.8	.87
Surgical status						
Elective	56.4	48.9	<.0001	54.4	53.9	.61
Semi-urgent	37.6	41.5		39.5	40.4	
Urgent	5.3	7.7		5.6	4.9	
Emergency	0.7	1.9		0.6	0.8	
Other procedure with CABG	11.2	15.7		12.2	12.6	.72

TABLE 6. Outcomes for propensity matched patients undergoing CABG

Outcomes	CCB	No CCB	OR	95% CI
Patient number	1726	1726		
In-hospital mortality (%)	0.75	1.45	0.48	0.23-0.98 (*P*=.044)
Morbidity (%)				
Dialysis	1.04	1.04	1.00	0.52-1.92 (*P*=1.00)
Low-output state	4.69	4.63	1.01	0.74-1.39 (*P*= .94)
Permanent pacemaker insertion	2.20	1.91	1.15	0.72-1.84 (*P*= .55)
Repeat operation	5.21	4.58	1.15	0.84-1.56 (*P*= .61)
Major bleeding	3.94	4.29	0.92	0.65-1.28 (*P*= .61)

CABG (OR, 0.66; 95% CI, 0.26-1.70; $P = .4$). The similarity in treatment effects observed in the meta-analysis and this observational study strengthens arguments that CCBs have important mortality benefits during cardiac surgery.

Our results argue against concerns that CCBs increase perioperative mortality, as suggested by Legault and coworkers.[23] Their RCT of nimodipine use during valve surgery was terminated early because of an excess of deaths in the CCB arm, largely caused by excessive bleeding. However, these patients all underwent hypothermic cardiopulmonary bypass. The latter inhibits platelet function,[24] whereas its effects on perioperative blood loss are

TABLE 7. Sensitivity analyses examining whether preoperative β-blockers influence the treatment effects of CCBs on CABG mortality

β-Blocker use	CCB OR for mortality (95% CI)	Included covariates	Regression model characteristics
Yes	0.52 (0.25-1.09)	Age, sex, left ventricular ejection fraction, timing of operation, procedure other than CABG, prior cardiac surgery	Area under ROC curve = 0.83 Hosmer-Lemeshow statistic $\chi^2 = 5.18$ ($P = .74$)
No	0.47 (0.18-1.19)	Age, sex, left ventricular ejection fraction, timing of operation, procedure other than CABG	Area under ROC curve = 0.83 Hosmer-Lemeshow statistic $\chi^2 = 2.64$ ($P = .92$)

mixed.[24,25] Furthermore, only 46% received aminocaproic acid, an antifibrinolytic agent that reduces blood loss during cardiac surgery by 30% to 40%.[26] By comparison, patients undergoing cardiac surgery at our hospital do not undergo hypothermic cardiopulmonary bypass and routinely receive antifibrinolytic agents. In contrast to the study by Legault and coworkers,[23] our analyses found no association between CCB use and major bleeding, thereby supporting a recent review that concluded that most of the clinical data linking CCBs and bleeding points against an increased risk.[27]

Study Limitations

Although this study used a variety of statistical methods to correct for confounders and selection biases, it is an observational study. Hence interpretation of results from this study should be limited to associations between variables of interest. No causal inferences should be drawn. Furthermore, cardiac surgical outcomes are confounded by a multitude of factors. The constraints of feasibility limit data collection in observational studies of this design; therefore all factors that determined preoperative CCB use might not have been collected. Although propensity scores reduce bias caused by observed covariates, they cannot remove confounding from these unobserved covariates. Only an RCT is able to do the latter.

Our analyses did not have sufficient power to determine whether CCBs benefit the subgroup receiving preoperative β-blockers. Nonetheless, our results suggest that the 2 medications have additive benefits, without any negative interactions. The logistic regression interaction term between CCBs and β-blockers was statistically nonsignificant. In addition, sensitivity analyses showed that preoperative β-blocker use did not affect the magnitude of benefits of CCBs among patients undergoing CABG.

Our data set did not allow us to determine the effects of different classes of CCBs: benzothiazepines (eg, diltiazem), phenylalkyamines (eg, verapamil), and dihydropyridines (eg, nifedipine and amlodipine). This is important given that dihydropyridines have been associated with increased mortality in nonsurgical studies.[28] In addition, we were not able to determine whether CCB therapy was continued throughout the immediate postoperative period. More than 50% of patients previously receiving CCBs might not receive them postoperatively.[29] The findings of the above meta-analysis,[4] however, suggest that ongoing CCB use intraoperatively and postoperatively would likely improve perioperative outcomes as well.

Finally, this study might have been affected by site confounding, given that our results reflect the effects of CCBs in a single tertiary care institution. Furthermore, the 1.8% perioperative mortality rate seen in this study contrasts with the 3.1% rate reported in a recent North American population-based study of CABG surgery.[11] The generalizability of our results to other hospitals will therefore require further study. It is nonetheless reassuring that CCBs have benefits even when baseline operative risks are relatively low.

Clinical Implications

CCBs remain relatively underused in cardiac surgical practice, largely because of the results of prior observational studies.[1-3] This observational study, using a larger sample size and more sophisticated risk-adjustment techniques, suggests instead that preoperative CCBs are associated with significant reductions in perioperative mortality. In light of a meta-analysis showing that intraoperative and postoperative CCB use significantly reduces MI and ischemia,[4] there is now strong justification for prospectively investigating perioperative CCB use among cardiac surgical patients. The most appropriate method for determining their efficacy is a large simple RCT, a feasible option given that 750,000 individuals annually undergo cardiac surgical procedures in the United States alone.[30] We would further suggest that this trial should target individuals undergoing CABG, the subgroup most likely to benefit from perioperative CCBs.

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